Cardiovascular Revascularization Medicine 16 (2015) 450–454

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Platelet inhibition with ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease with or without diabetes mellitus

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ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 6 August 2015
Accepted 13 August 2015

Keywords:
Ticagrelor
Clopidogrel
Diabetes mellitus
Hispanic

ABSTRACT

Background/purpose: Diabetes mellitus (DM) disproportionately affects Hispanic patients. DM patients have enhanced platelet reactivity and reduced sensitivity to clopidogrel. Ticagrelor demonstrated a more rapid onset and greater magnitude of platelet inhibition than clopidogrel in Hispanic patients with stable coronary artery disease (CAD). This subgroup analysis examined the onset and level of platelet inhibition of ticagrelor and clopidogrel in Hispanic patients with DM.

Methods/materials: This was a subgroup analysis of a randomized, open-label, crossover study in which 40 Hispanic patients with stable CAD received ticagrelor 180 mg loading dose (LD)/90 mg twice-daily maintenance dose (MD) then clopidogrel 600 mg LD/75 mg once-daily MD, or vice versa. The primary end point was on-treatment platelet reactivity at 2 hours post-LD using the VerifyNow™ P2Y12 test.

Results: 21 patients had DM and 19 were non-diabetic. At 2 hours post-LD, mean platelet reactivity in the diabetic group was 34.5 PRU with ticagrelor versus 219.3 PRU with clopidogrel ($P < 0.001$), and in the non-diabetic group was 33.7 PRU with ticagrelor versus 181.0 PRU with clopidogrel ($P < 0.001$). In both diabetic and non-diabetic subgroups, mean platelet reactivity declined to a significantly greater extent with ticagrelor than clopidogrel at all time points evaluated (0.5, 2, and 8 hours post LD and after 7–9 days of MD). Patients were significantly more likely to have high on-treatment platelet reactivity (≥208 PRU) during treatment with clopidogrel compared with ticagrelor, regardless of diabetic status.

Conclusions: Among Hispanic patients with stable CAD, ticagrelor achieves a faster onset and greater magnitude of platelet inhibition compared with clopidogrel, irrespective of diabetic status.

1. Introduction

The prevalence of diabetes mellitus (DM) is expected to continue increasing, with some estimates suggesting that one third of the US adult population will be affected by diabetes by 2050 [1]. However, the burden of diabetes is not evenly spread across the US population, with a disproportionately high prevalence among ethnic minorities, including Hispanics [2,3], and those at the lowest income and educational levels [4]. Diabetes is the fifth leading cause of death among Hispanic Americans and, compared with non-Hispanic white adults, the risk of developing DM is 66% higher among Hispanic/Latino adults [3].

Patients with DM have high platelet reactivity [5–7], which contributes to a high incidence of coronary artery disease (CAD) in these individuals. Studies show that patients with diabetes have a more than three-fold higher risk of developing fatal CAD compared with non-diabetic individuals, which may be associated with the clustering of cardiovascular risk factors in patients with diabetes [8]. This highlights the importance of effective primary and secondary preventive therapies in diabetic patients to minimize the risk. However, diabetes may also affect response to treatment. For example, diabetic patients show a reduced responsiveness to the $P2Y_{12}$ inhibitor clopidogrel compared with non-diabetic patients [5], and this reduced responsiveness is linked to worse cardiovascular outcomes [9].

Ticagrelor is an orally administered, direct-acting, reversibly binding $P2Y_{12}$ receptor antagonist that inhibits adenosine diphosphate (ADP)-induced platelet aggregation [10,11]. Ticagrelor differs from clopidogrel in that it is not a prodrug and does not require conversion by hepatic metabolism to be active [10,12]. Another key difference between the two agents is that ticagrelor has also been shown to inhibit cellular uptake of adenosine via inhibition of the equilibrative nucleoside transporter 1 (ENT1), whereas clopidogrel has not [13].

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http://dx.doi.org/10.1016/j.carrev.2015.08.007

Ticagrelor is approved for use, in combination with low-dose aspirin (75–100 mg/day), to prevent atherothrombotic events in patients with acute coronary syndrome (ACS) [14], based on its efficacy and safety over 12 months of follow-up in the large-scale, randomized, phase III PLATelet inhibition and patients Outcomes (PLATO) trial [15]. A substudy of the PLATO trial found that ticagrelor reduced the incidence of ischemic events compared with clopidogrel in patients with DM in a manner consistent with the results of the overall PLATO cohort. [16] These data suggest that ticagrelor may be a suitable alternative to clopidogrel for patients with diabetes.

We have previously conducted a multicenter, open-label, randomized, multiple-dose, crossover study in Hispanic patients with documented CAD, and found that platelet reactivity was more strongly inhibited by ticagrelor than clopidogrel [17]. The inclusion of a high proportion of diabetic patients in this study provided the opportunity to study the effects of ticagrelor or clopidogrel in Hispanic patients with and without diabetes. Therefore, the objectives of the current substudy were to compare on-treatment platelet reactivity during treatment with ticagrelor versus clopidogrel in Hispanic CAD patients with and without DM, and to assess the safety profile of ticagrelor in this patient group.

2. Materials and methods

This was a subgroup analysis of a randomized, open-label, crossover study conducted at 6 US centers between April 2012 and May 2013 (clinicaltrials.gov identifier, NCT01523366). The complete methods have been published previously [17]. Briefly, the study included adults aged ≥18 years, who self-identified as Hispanic, had documented stable CAD based on having stable angina pectoris, or a history of MI, or revascularization, and were receiving aspirin 75–100 mg/day. The diabetic status of each patient was assessed at randomization. Patients with DM were eligible for enrolment if they had a glycosylated hemoglobin (HbA1c) level of <10%. Patients at increased risk of bleeding were excluded from the study, as were patients who had any indication for oral anticoagulant or dual antiplatelet therapy, and those taking strong cytochrome P450 (CYP) 3A4 inhibitors or inducers. Other exclusion criteria have been described in detail previously [17].

The study was approved by the Institutional Review Boards at all sites, and conducted in accordance with the provisions of the Declaration of Helsinki and AstraZeneca policy on bioethics. All patients provided written informed consent prior to study entry.

Patients were randomized 1:1 to receive open-label treatment in two possible sequences: clopidogrel first and ticagrelor second, or vice versa, each for 7–9 days, separated by a 10- to 14-day washout period (Fig. 1). During each active treatment period, patients received a single loading dose (LD) followed by maintenance dosing (MD) for 7–9 days, in addition to their usual daily aspirin dose of 75–100 mg. Clopidogrel doses were 600 mg for LD and 75 mg once daily for MD; ticagrelor doses were 180 mg for LD and 90 mg twice daily for MD.

Each patient made eight visits to the study center during the 11-week study. Screening was conducted at visit 1 and randomization at visit 2, then three visits occurred during each treatment period, and one follow-up visit at 7–10 days after the final treatment visit.

Blood samples were taken for analysis of platelet reactivity at baseline prior to LD, and at 0.5, 2, and 8 hours after the LD. In addition, samples were taken just prior to, and 2 and 8 hours after the last morning dose of both agents, as well as 12 hours after the last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel. During the ticagrelor treatment period, blood samples were drawn at the same time as the platelet reactivity samples, to measure plasma concentrations of ticagrelor and its active metabolite AR-C124910XX.

Platelet reactivity was assessed using the VerifyNow® P2Y12 test (Accumetrics, San Diego, CA), a validated measure of ADP-induced platelet aggregation [18,19]. In this assay, $P2Y_{12}$-mediated reactivity is expressed in $P2Y_{12}$ reaction units (PRU), with higher values reflecting greater reactivity. Study personnel were blinded to the PRU results.

The primary end point of the substudy was the inhibition of platelet reactivity with ticagrelor versus clopidogrel 2 hours after LD, by DM status. Secondary end points included the PRU at other time points by DM status, and the safety of ticagrelor in Hispanic patients with versus without diabetes. Safety and tolerability were assessed by the incidence and severity of adverse events, and by assessment of clinical laboratory parameters, physical examination, 12-lead electrocardiograph (ECG) and vital signs.

2.1. Statistical analysis

A pretrial estimate showed that a sample size of 12 patients would provide 90% power to detect a difference of 100 PRUs in the primary end point between ticagrelor and clopidogrel, assuming a standard deviation (SD) of 93 PRU, a correlation of 0.5 between paired observations and a 2-sided alpha level of 0.05. However, it was planned that 34 patients would be enrolled to ensure 28 evaluable patients, which would provide >99% power to detect the anticipated primary outcome effect. This sample size would also provide sufficient power to evaluate $P2Y_{12}$ inhibition at secondary time points, within the subgroups of patients with versus without diabetes, and provide a larger sample size for analysis of potential adverse events.

Categorical variables were reported as counts and percentages, and continuous variables as mean ± SD. The primary end point, PRU analysis, was undertaken using a mixed-effect model with terms for treatment period, treatment sequence and a random effect for patient within sequence. Mean on-treatment reactivity was estimated using least squares means and 2-sided 95% confidence intervals (CIs). Data were analyzed in each group of patients with versus without diabetes

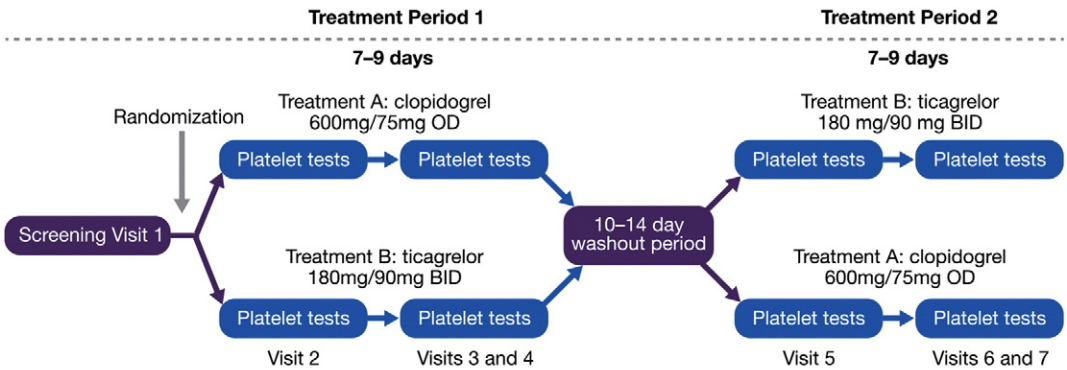

Fig. 1. Study design. Taken from *J Thromb Thrombolysis* 2015;39:8–14 [17](with permission). BID, twice daily; QD, once daily.

and the results compared. An exploratory analysis was undertaken to evaluate the percentage of patients with high on-treatment platelet reactivity (defined as ≥208 PRU, according to recent expert consensus recommendations) [20] in the ticagrelor versus clopidogrel groups, at all time points, and this comparison used Fisher's exact test.

Pharmacodynamic assessments were undertaken on all patients who had valid PRU data available and no major protocol violations, and safety assessments were undertaken on all patients who received at least one dose of study medication. Safety was evaluated using descriptive statistics.

3. Results

Of the 40 patients who were randomized to treatment, 38 patients received both ticagrelor and clopidogrel, and completed the study. One patient randomized to receive ticagrelor withdrew consent and discontinued the study during ticagrelor treatment. In addition, one patient successfully completed ticagrelor treatment and crossed over to clopidogrel, but did not complete clopidogrel treatment. Of the 40 randomized patients, 21 patients (52.5%) had Type 2 DM and 19 (47.5%) were non-diabetic. Demographic and clinical characteristics are shown in Table 1. The diabetic subgroup included more females (42.9%) compared with the non-diabetic subgroup (15.8%). Patients without diabetes were slightly older than diabetic patients (mean ± SD: 65.7 ± 8.1 years in non-diabetic patients versus 62.0 ± 9.3 years in diabetic patients), and had a lower bodyweight (mean: 77.8: ± 12.9 kg) and BMI (median: 28.8 kg/m^2) compared with the diabetic subgroup (mean weight: 87.9 ± 17.6 kg and median BMI: 30.5 kg/m^2).

In the diabetic subgroup, baseline mean ± SD platelet reactivity was 282.7 ± 58.8 PRU before ticagrelor, and 298.5 ± 50.1 PRU before clopidogrel. Baseline platelet reactivity was a little lower in the non-diabetic subgroup: mean ± SD 260.7 ± 74.9 PRU before ticagrelor and 258.3 ± 61.6 PRU before clopidogrel. Analysis of platelet inhibition over time showed that ticagrelor provided a faster onset and greater extent of platelet inhibition compared with clopidogrel, regardless of diabetic status (Fig. 2). At 2 hours post-LD, ticagrelor treatment was associated with significantly lower platelet reactivity compared with clopidogrel treatment in diabetic patients (mean: 34.5 ± 33.5 PRU with ticagrelor versus 219.3 ± 84.3 PRU with clopidogrel, $P < 0.001$) and in non-diabetic patients (mean: 33.7 ± 30.4 with ticagrelor versus 181.0 ± 89.2 PRU with clopidogrel, $P < 0.001$). There was no significant interaction between the treatment effect and diabetes status ($P = 0.13$). At all time points evaluated, ticagrelor treatment lowered platelet reactivity to a significantly greater extent than clopidogrel did, in both the diabetic and non-diabetic subgroups (Fig. 2).

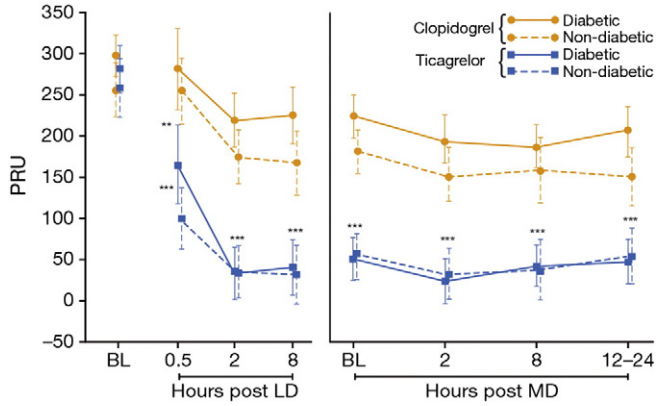

Fig. 2. Platelet reactivity expressed in $P2Y_{12}$ reaction units (PRU) at each measured time point after ticagrelor or clopidogrel in diabetic patients and non-diabetic patients. The left-hand panel presents PRU post-loading dose (LD) and the right-hand panel presents PRU following the last morning dose after 7–9 days of ticagrelor 90 mg BID or clopidogrel 75 mg OD. $^{**}P < 0.05$, $^{***}P < 0.001$ versus clopidogrel at 30-minute time point. Values connected by solid or dotted lines are the least-squares mean and 95% confidence interval from mixed effect models at each time point. The individual values plotted at baseline (BL) are the observed mean and 95% CI for the mean, and were not obtained from the models that the other estimates are based upon. Patients with low BL PRU values (indicating an incomplete washout from anti-platelet therapy) are excluded during the period corresponding to the low BL value.

A higher proportion of patients showed high on-treatment platelet reactivity (≥208 PRU) with clopidogrel than with ticagrelor, irrespective of diabetic status (Fig. 3). At 2 hours after the clopidogrel LD, 66.1% of the diabetic subgroup and 37.5% of the non-diabetic subgroup had a PRU of ≥208, whereas at 2 hours after the ticagrelor LD, PRU was <208 in all patients, irrespective of diabetic status.

3.1. Safety and tolerability

Both study treatments were generally well tolerated, and no deaths, serious adverse events (AEs) or severe AEs were reported after either ticagrelor or clopidogrel. In addition, no bleeding events were reported in either group. Eleven patients (27.5%) experienced at least one AE; 7 patients in the diabetic subgroup (33.3%) and 4 in the non-diabetic subgroup (21.1%). Most AEs were mild in intensity (Table 2), but two moderate intensity AEs occurred: one case of increased heart rate in a non-diabetic patient receiving ticagrelor and one case of a fall in a diabetic patient receiving clopidogrel. No patients discontinued study medication due to an AE, and no clinically relevant changes in physical examinations or vital signs were reported during the study.

Table 1
Baseline demographics and clinical characteristics in the diabetic and non-diabetic cohorts of Hispanic CAD patients.

	Diabetic subgroup (n = 21)	Non-diabetic subgroup (n = 19)
Ethnicity, n (%)		
Hispanic or Latino	21 (100.0)	19 (100.0)
Diabetes, n (%)		
Diabetes mellitus Type I	–	–
Diabetes mellitus Type II	21 (100.0)	–
Mean (SD) age, years	62.0 (9.3)	65.7 (8.1)
Age ≥65 years, n (%)	8 (38.1)	10 (52.6)
Gender, n (%)		
Male	12 (57.1)	16 (84.2)
Female	9 (42.9)	3 (15.8)
Mean weight (SD), kg	87.9 (17.6)	77.8 (12.9)
Median (range) BMI, kg/m^2	30.5 (25.2–42.9)	28.8 (20.4–39.7)
Obesity (BMI >30 kg/m^2), n (%)	11 (52.4)	6 (33.3)
Cardiovascular risk factors, n (%)		
Hypertension	20 (95.2)	18 (94.7)
Dyslipidemia*	20 (95.2)	19 (100.0)
Medical history, n (%)		
Previous MI	12 (57.1)	14 (73.7)
Previous PCI	17 (81.0)	15 (78.9)
CABG	7 (33.3)	6 (31.6)
Stable angina pectoris	6 (28.6)	2 (10.5)
Congestive heart failure	1 (4.8)	2 (10.5)
Renal disease	0 (0)	1 (5.3)

*Including hypercholesterolemia.
BMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

4. Discussion

According to the 2012 US Census Bureau estimates, almost 17% of the US population were Hispanic or Latino [21], and this population group is at particularly high risk of developing Type 2 DM [3]. Moreover, the number of cardiovascular risk factors, including DM, tends to be disproportionately higher among Hispanic individuals in the lowest socioeconomic or educational groups, and among those who have lived longer in the US and are more acculturated to the US way of life [22]. Previous studies have shown that patients with DM have a reduced response to clopidogrel treatment [5], so it was important to determine whether there was an interaction between DM and the antiplatelet

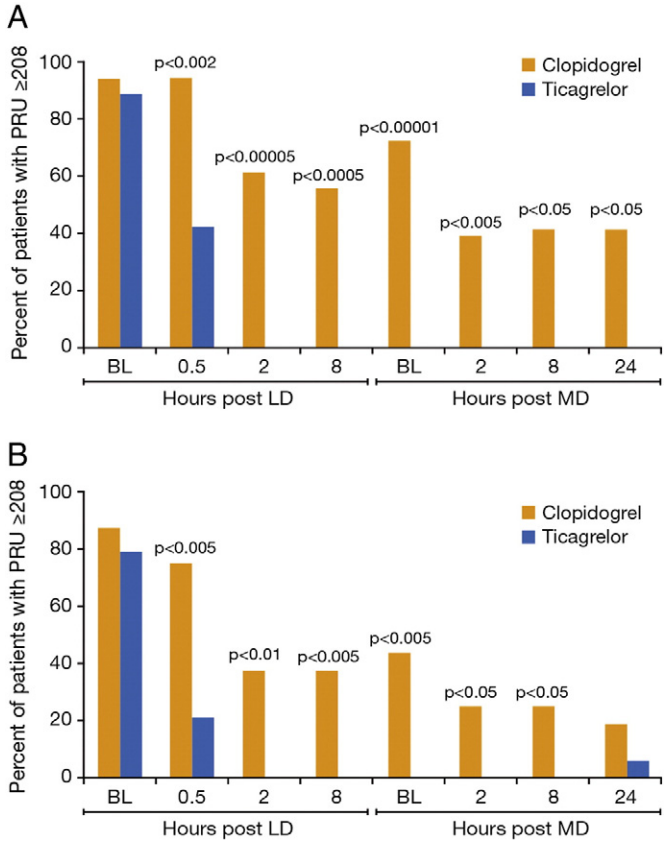

Fig. 3. Percentage of patients with high on-treatment platelet reactivity defined as a PRU ≥ 208 in (a) diabetic patients, and (b) non-diabetic patients receiving ticagrelor and clopidogrel. Baseline (BL); $P2Y_{12}$ reaction units (PRU); Loading dose (LD); Maintenance dose (MD); $P =$ Fisher's exact test P value (2-tail) for ticagrelor versus clopidogrel.

activity of the newer $P2Y_{12}$ inhibitor ticagrelor among Hispanic patients with diabetes.

Our study had previously demonstrated that ticagrelor has a faster onset and greater extent of platelet inhibition compared with clopidogrel in Hispanic patients with CAD [22]. The current subgroup analysis confirmed that this was also the case in Hispanic CAD patients with or without diabetes. At 2 hours after the LD, patients in both the diabetic and non-diabetic subgroups showed significantly lower platelet reactivity after ticagrelor compared with clopidogrel, as measured by PRU. Similarly, at all on-treatment time points following the LD, and throughout the maintenance dosing period, platelet reactivity remained significantly lower after ticagrelor than clopidogrel. These findings are consistent with previous data from a similar study among African-American patients with stable CAD [23], and with findings in a mixed race population of patients, 88% of whom were Caucasian [24].

The overall study also demonstrated that patients receiving clopidogrel treatment were significantly more likely to show high on-treatment platelet reactivity (≥208 PRU) compared with patients receiving ticagrelor [17], and this was also true in the diabetic and non-diabetic subgroups. A similar lack of high on-treatment platelet reactivity with ticagrelor has been demonstrated in African Americans with stable CAD [23].

Although high platelet reactivity has long been shown to be associated with ischemic events, the link between low on-treatment platelet reactivity and bleeding is less clear. Tantry et al [20] proposed cut-off values for both high and low on-treatment platelet reactivity, based on various platelet function assays, adding further to the hypothesis that there exists a therapeutic window of optimal on-treatment platelet reactivity that could potentially play a role in future studies.

The more consistent antiplatelet effect of ticagrelor relative to clopidogrel among diabetic and non-diabetic patients in the current study may explain the significant improvement in cardiovascular outcomes seen with ticagrelor in the PLATO study [16]. The analysis of outcomes among the diabetic and non-diabetic patients in PLATO showed that ticagrelor reduced the risk of the primary end point (a composite of cardiovascular death, MI or stroke) by 17% (hazard ratio [HR]: 0.83, 95% CI: 0.74–0.93) in patients without diabetes and by 12% (HR: 0.88, 95% CI: 0.76–1.03) in patients with diabetes, relative to clopidogrel, and that there was no significant increase in overall major bleeding complications [16]. No significant interaction for diabetes status was noted with respect to the primary composite outcome in the PLATO study [16], a finding that has also been demonstrated with the $P2Y_{12}$ inhibitor prasugrel in diabetic and non-diabetic patients in the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) [25].

A poor response to clopidogrel among DM patients is not related to glycemic control [26,27], but appears to be the result of reduced circulating levels of the drug's active metabolite [28–30]. Diabetic patients with moderate-severe chronic kidney disease also have reduced response to clopidogrel and a higher prevalence of on-treatment platelet reactivity compared with diabetic patients in whom renal function is normal [31]. Impaired renal function is unlikely to have been the cause of the low platelet response to clopidogrel in our study, because renal disease was present in only one patient, who from past medical history was not diabetic.

The safety profile of ticagrelor was similar and consistent in both the diabetic and non-diabetic subgroups of Hispanic patients in our study. The overall safety profile of ticagrelor in the present study was consistent with that seen in other studies in patients with stable CAD, including African-American [23] and mixed race cohorts [24].

Our study is not without limitations. First, treatment was administered in an open-label fashion which has the potential to introduce bias. However, we tried to minimize the potential for bias by using an objective assessment of platelet function and by blinding study personnel to the PRU results. Second, the study included relatively few patients. However, in order to allow for adequate assessment of subgroups, we deliberately enrolled more patients than was needed, based on the pretrial assessment of the required sample size. In addition, we tried to minimize the potential for variation by randomizing patients to different treatment sequences and using each patient as their own control.

In conclusion, ticagrelor treatment provided a faster onset and greater extent of platelet inhibition compared with clopidogrel in

Table 2
Adverse events.

Patients, n (%)	Diabetic subgroup (n = 21)		Non-diabetic subgroup (n = 19)	
	Ticagrelor (n = 21)	Clopidogrel (n = 21)	Ticagrelor (n = 19)	Clopidogrel (n = 18)
Any adverse event	3 (14.3)	1 (19.0)	2 (10.5)	2 (11.1)
Diarrhea	1 (4.8)	0 (0.0)	–	–
Upper abdominal pain	0 (0.0)	1 (4.8)	–	–
Irregular heart rate	1 (4.8)	0 (0.0)	–	–
Increased heart rate	–	–	1 (5.3)	0 (0.0)
Oropharyngeal discomfort	–	–	1 (5.3)	0 (0.0)
Dyspnea	1 (4.8)	0 (0.0)	1 (5.3)	0 (0.0)
Malaise	–	–	1 (5.3)	0 (0.0)
Headache	1 (4.8)	1 (4.8)	0 (0.0)	1 (5.6)
Dizziness	–	–	1 (5.3)	0 (0.0)
Dysgeusia	–	–	1 (5.3)	0 (0.0)
Burning sensation	1 (4.8)	0 (0.0)	–	–
Fall	0 (0.0)	2 (9.5)	–	–
Rib fracture	0 (0.0)	1 (4.8)	–	–
Musculoskeletal chest pain	1 (4.8)	0 (0.0)	–	-
Nasopharyngitis	–	–	0 (0.0)	1 (5.6)

Hispanic patients with CAD, irrespective of diabetic status. Ticagrelor treatment could prove beneficial in Hispanic CAD patients with ACS.

Disclosures

This study was funded by AstraZeneca, who, with consultation, designed the study and completed the data collection. In addition, AstraZeneca contributed to the interpretation of the data, the preparation of this manuscript and the decision to submit the article for publication. The authors retained full responsibility for the content of the manuscript and made the final decision to submit the article for publication.

Dr LC Clavijo reports receipt of consulting honoraria from AstraZeneca and Medtronic, Speaker's fees from Daiichi-Sankyo/Eli Lilly and Medtronic, and received institutional grant support from AstraZeneca, Abbott Vascular, Medtronic and Roche. MJ Price receives consulting honoraria from AstraZeneca, Daiichi-Sankyo/Eli Lilly & Co., Janssen Pharmaceuticals, Medicure, and The Medicines Company, speaker's fees from AstraZeneca and Daiichi-Sankyo/Eli Lilly & Co., and equity interest in Iverson Genetics. DJ Angiolillo has received payment as an individual for: a) Consulting fee or honorarium from Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular and PLx Pharma; b) Participation in review activities from CeloNova, Johnson & Johnson, and St. Jude Medical. Institutional payments for grants from Glaxo-Smith-Kline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Janssen Pharmaceuticals, Inc., Osprey Medical, Inc., Novartis, CSL Behring, and Gilead. G Carlson and R Teng are employees of AstraZeneca, LP. J Maya and R Caplan were employed by AstraZeneca, LP at the time of study completion.

Acknowledgments

Medical writing support was provided by Lisa Michel of Gardiner-Caldwell Communications, and was funded by AstraZeneca.

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